Remarks/Arguments:

Claims 6-21, presented hereby, are pending.

Claims 1-5 are canceled, hereby, without prejudice or disclaimer.

Support for the newly presented claims is found in the original claims and in the specification at page 2, lines 8-12, and in the paragraph bridging pages 2 and 3.

The subject application is a continuation of Application Serial No. 09/355,931, which was under final rejection. The present claims contain, *inter alia*, subject matter found in the parent application claims of record subject to final rejection.

According to the final Office Action (mailed March 19, 2003) in the parent application, the claims of record stood rejected under 35 USC 112, second paragraph, as allegedly be indefinite. The rejection does not apply against the present claims.

According to the statement of rejection, the phrase "an effective amount" allegedly rendered the claims indefinite because "claims do not recite the condition which is treated" (final office action, page 2). This is not the case with the present claims.

The present claims provide a "method of rendering skin or mucosa permeable to the compound 2,3-dimethoxy-5-methyl-6-decaprenyl-1,4-benzoquinone (Q10)" by administration of Q10 together with "an effective amount of protein-containing pulmonary surfactant," i.e., an amount of protein containing surfactant sufficient to effect "rendering skin or mucosa permeable" to Q10. Further in accordance with the statement of rejection under section 112, second paragraph, it is alleged that the recited "combined with liposomes" renders the reciting claim indefinite. The phrase

is alleged to be indefinite, apparently, because the claim does not recite whether :"the components [are] encapsulated [by liposomes] or [there are] just empty liposomes combined with the composition" (final office action page 3). The rejection is poorly taken, because it concerns *how* the invention is to be practiced.

The statement of rejection confuses the function of the claims, on the one hand, with the function of the specification, on the other; the claims define the legal limits of the invention, the specification details *how* the invention is to be *practiced. In re Roberts*, 176 USPQ 313, 315 (CCPA 1973). Explaining *how* the invention is to be practiced is the function of the specification; the function of the claims is to define the legal limits of the invention. *In re Roberts*, 176 USPQ 313, 315 (CCPA 1973). Merely that it requires some thought to understand the meaning of a claim term does not render the term indefinite under §112, ¶2.

> The purpose of the claims is not to explain the technology or how it works, but to state the legal boundaries of the patent grant. A claim is not "indefinite" simply because it is hard to understand when viewed without benefit of the specification.

S3 Inc. v. nVIDIA Corp., 59 USPQ2d 1745, 1748 (Fed. Cir. 2001).

Still further recording to the statement of rejection, the term "neutrolipid" allegedly renders the reciting claim indefinite, because it is allegedly unclear whether the term means "neutrolipid" (final office action page 3). Contrary to the allegation contained in the statement of rejection, one of ordinary skill in the art would not be confused as to the meaning of "neutrolipid" and would readily recognize that the term means the same as "neutrolipid". The standard for determining indefiniteness under section 112, paragraph 2, is whether one of ordinary skill in the art would be

confused as to the scope of the claim terminology at issue. *In re Kroekel*, 183 USPQ 610 (CCPA 1974). Moreover, that it might require some thought to understand the meaning of the claim term does not render the term indefinite under section 112, paragraph 2. *S3 Inc.*, 59 USPQ2d at 1748.

According the the final Office Action the claims of record stood rejected-type double patenting based on claims 1-4 of U.S. Patent No. 6/228,891. The Terminal Disclaimer submitted herewith, renders the issue moot.

According to item 6 of the final Office Action, all claims were rejected under 35 USC 103(a) as allegedly unpatentable over Neigut in view of Pavani and Wong. The rejection is not applicable against the present claims.

First of all, the rejection is not applicable against the present claims since the statement of rejection relies on the allegation that a lung-surfactant extract that contains proteins is equivalent to a lung-surfactant extract that does not contain proteins (Office Action page 6, first complete paragraph). The statement of rejection relies on the teachings of Wong at column 2, lines 42-46, as the basis for this allegation. The passage at issue in Wong reads"such a surfactant may be extracted . . . which [extract] may or may not contain SP-A, SP-B and SP-C (surfactant proteins -A, -B, -C)." In other words, the rejection maintains that the "surfactant" that "may not contain . . . surfactant proteins -A, -B, -C" is a lung-surfactant extract that does not contain *any* proteins; however, the rejection is mistaken.

The statement of rejection relies on the mistaken assumption that "surfactant proteins -A, -B, -C" are the only proteins in lung surfactant, which is incorrect. There is at least one additional

protein in lung surfactant, i.e., surfactant protein D (SP-D), as evidenced by Shrive, et al., *Journal of Molecular Biology, 331*, 509-523, 2003 (online abstract attached, hereto).

Since "surfactant proteins -A, -B, -C" are not the only proteins in lung surfactant, the "surfactant" that "may not contain . . . surfactant proteins -A, -B, -C" is *not* a lung-surfactant extract that does not contain *any* proteins. As a result, Wong does *not* teach that a lung-surfactant extract that contains proteins is equivalent to a lung-surfactant extract that does not contain proteins.

Accordingly, the cited references do not evidence obviousness under §103(a), notwithstanding statements to the contrary in the final Office Action. The "evidence upon which the examiner relies must clearly indicate that a worker of routine skill in this art would view the claimed invention as being obvious." *Ex parte Wolters*, 214 USPQ 735, 736 (BPA&I 1982). "It is facts which must support the legal conclusion of obviousness." *Ex parte Crissy*, 201 USPQ 689, 695 (POBdApp 1976).

> The Patent Office has the initial duty of supplying the factual basis for its rejection. It may not, because *it* may *doubt* that the invention is patentable, resort to speculation, unfounded assumptions or hindsight reconstruction to supply deficiencies in the factual basis.

In re Warner, 154 USPQ 173, 178 (CCPA 1967) (*emphasis in original*). An argument by the USPTO is "not prior art." *In re Rijckaert*, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993). When the

> USPTO asserts that there is an explicit or implicit teaching or suggestion in the prior art, it must indicate where such a teaching or suggestion appears *in the reference*. . . . The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient to establish inherency. . . . [S]uch a retrospective view of inherency is not a substitute for some teaching or suggestion supporting an obviousness rejection.

28 USPQ2d at 1957 (*emphasis added*).

Secondly, the rejection under §103(a) is not applicable against the present claims since the combination of Pavani and Wong, as alleged in the statement of rejection, is contraindicated.

Neigut teaches a topical application containing coenzymeQ (CoQ), but is silent with respect to natural lung surfactant. Pavani is silent with respect to CoQ, but teaches the use of a *component* of pulmonary surfactant. According to Pavani, pulmonary surfactant is a complex mixture formed by simple sugars and phospholipids (Pavani column 1, lines 50 to 53). That is, according to the understanding of Pavani, pulmonary surfactant does not contain protein.

Pavani further teaches that *fractions* of pulmonary surfactant activate macrophages (Pavani column 1, line 60, to column 2, line 3). The invention of Pavani is to use the (pure) compound 1,2-dipalmitoyl-L-α-phosphatidyl-N,N-dimethylethanolamine *instead* of fractions of pulmonary surfactant.

Wong is relied on as allegedly showing that the compound used by Pavani is a major lipid component of pulmonary surfactant and, therefore, one skilled in the art would have considered it obvious to replace the purified compound used by Pavani with the complete (non-fractionates) pulmonary surfactant, which is just the opposite of the teachings of Pavani. In other words, Pavani teaches away from Wong. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994). References taken in combination teach away when the

combination would produce a "seemingly inoperative device." *In re Sponnoble*, 160 USPQ 237, 244 (CCPA 1969). A "reference teaches away if it leaves the impression that the product would not have the property sought by the applicant." 32 USPQ2d at 1132, citing with approval *In re Caldwell*, 138 USPQ 243, 245 (CCPA 1963).

Therefore, not only is the combination of Neigut and Pavani taken without the necessary motivation to combine them, combining Neigut and Pavani with Wong is contraindicated, because Pavani teaches away from Wong. The totality of each reference's teachings must be considered when combining those teachings with the rest of the prior art. *W. L. Gore & Assoc., Inc. v. Garlock, Inc.*, 220 USPQ 303, 311 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984).

> It is impermissible within the framework of §103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciate of what such reference fairly suggests to one of ordinary skill in the art.

In re Hedges, 228 USPQ 685, 687 (Fed. Cir. 1986). "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988).

> It is impermissible within the framework of §103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.

In re Hedges, 228 USPQ 685, 687 (Fed. Cir. 1986). It is the combined teachings of the prior art, taken as a whole, which must be considered in an obviousness analysis. *Ryko Manufacturing Co. v. Nu-Star, Inc.*, 21 USPQ2d 1053 (Fed. Cir. 1991).

> When prior art references require selective combination by the court to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight gleaned from the invention itself. . . There must be :something in the prior art to suggest the desirability, and thus the obviousness, of making the combination." [*Citation omitted.*]

Interconnect Planning Corp. v. Feil, 227 USPQ 543 (Fed. Cir. 1985).

For the foregoing reasons, the rejection under 35 USC 103 of record in the (final Office Action) of the parent application is not applicable against the present claims in the subject continuation application.

Request for Acknowledgment of Foreign Priority Under 35 USC 119

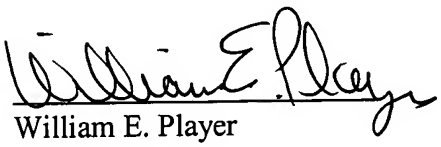
A claim to foreign priority under 35 USC 119 has been made (inventorship declaration, filed February 23, 2004) and the certified copy of the priority document received by the PTO (Notification of Acceptance, mailed October 27, 1999, by the PTO in parent application no. 09/355,931, and Form PCT/IB304, mailed 20 May 1998 by the International Bureau, of record in the parent application).

Accordingly, request is made that the Examiner mark the next Office Action to acknowledge, both, the claim to §119 priority and receipt of the certified copy.

Favorable action is requested.

Respectfully submitted,

JACOBSON HOLMAN PLLC

By 
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Journal of Molecular Biology
Volume 331, Issue 2 , 8 August 2003, Pages 509-523

doi:10.1016/S0022-2836(03)00761-7 Cite or link using doi

High-resolution Structural Insights into Ligand binding and Immune Cell Recognition by Human Lung Surfactant Protein D

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Received 26 February 2003; revised 9 June 2003; accepted 11 June 2003; Edited by A. Klug
Available online 22 July 2003.

Abstract

Lung surfactant protein D (SP-D) can directly interact with carbohydrate residues on pulmonary pathogens and allergens, stimulate immune cells, and manipulate cytokine and chemokine profiles during the immune response in the lungs. Therapeutic administration of rfhSP-D, a recombinant homotrimeric fragment of human SP-D comprising the α-helical coiled-coil neck plus three CRDs, protects mice against lung allergy and infection caused by the fungal pathogen *Aspergillus fumigatus*. The high resolution crystal structures of maltose-bound rfhSP-D to 1.4 Å, and of rfhSP-D to 1.6 Å, define the fine detail of the mode and nature of carbohydrate recognition and provide insights into how a small fragment of human SP-D can bind to allergens/antigens or whole pathogens, and at the same time recruit and engage effector cells and molecules of humoral immunity. A previously unreported calcium

ion, located on the trimeric axis in a pore at the bottom of the funnel formed by the three CRDs and close to the neck–CRD interface, is coordinated by a triad of glutamate residues which are, to some extent, neutralised by their interactions with a triad of exposed lysine residues in the funnel. The spatial relationship between the neck and the CRDs is maintained internally by these lysine residues, and externally by a glutamine, which forms a pair of hydrogen-bonds within an external cleft at each neck–CRD interface. Structural links between the central pore and the cleft suggest a possible effector mechanism for immune cell surface receptor binding in the presence of bound, extended natural lipopolysaccharide and phospholipid ligands. The structural requirements for such an effector mechanism, involving both the trimeric framework for multivalent ligand binding and recognition sites formed from more than one subunit, are present in both native hSP-D and rfhSP-D, providing a possible explanation for the significant biological activity of rfhSP-D.

Author Keywords: lung surfactant protein; high-resolution structure; collectin; carbohydrate recognition

Abbreviations: SP-D, lung surfactant protein D; SP-A, lung surfactant protein A; hSP-D, human lung surfactant protein D; hSP-A, human lung surfactant protein A; rfhSP-D, recombinant fragment of human lung surfactant protein D; MBL, mannan binding lectin; PEG, polyethyleneglycol; MBP, mannose binding protein; CRD, carbohydrate recognition domain; MPD, 2,4-methylpentane diol

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Journal of Molecular Biology
Volume 331, Issue 2 , 8 August 2003 , Pages 509-523